Hovedoppgave

NTNU
Norges teknisk-naturvitenskapelige universitet

Heidi Hammer Eriksen

Risk factors for cerebral infarction in a general population aged 50-66 years

HUNT3 MRI

Hovedoppgave i Medisinstudiet
Veileder: Asta Kristine Håberg
Januar 2022

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I Summaries

Norsk sammendrag

Målet med denne tverrsnittstudien var å undersøke ulike risikofaktorer for hjerneinfarkt i en generell populasjon. Kliniske og stille (synlige på MR-bilder) infarkter ble analysert som én gruppe i denne oppgaven. Risikofaktorene inkludert i studien var både kliniske faktorer og ulike radiologiske funn forbundet med hjernens helse.

I HUNT3 MRI-studien ble 1006 deltakere fra en generell populasjon inkludert. Aldersspennet var fra 50 til 66 år, og de hadde noe bedre helse sammenlignet med kontroller. Radiologiske mål inkludert var hvit substans hyperintensiteter (målt med Fazekas skala) og cerebrale mikroblødninger. Kliniske risikofaktorer inkludert i studien var hypertensjon, overvekt basert på kroppsmasseindeks og midje-hofte-mål, diabetes mellitus, metabolsk syndrom, røyking og inflammasjonsnivå.

Blant deltakerne i HUNT3 MRI-studien fant vi kun en sammenheng mellom alder og mengden hvit substans hyperintensiteter og økt prevalens av hjerneinfarkt. For mer kunnskap om risikoen for hjerneinfarkt i løpet av en livstid, anbefales videre oppfølgingsstudier når datainnsamlingen fra HUNT4 MR er komplett.

English summary

The aim of this cross-sectional observational study was to investigate several risk factors of cerebral infarctions in a general population. In this thesis, clinical and silent (detectable with neuroimaging) infarctions were analyzed as one group. Risk factors included are both clinical factors and some brain health factors identifiable with neuroimaging.

In HUNT3 MRI-study, participants from a general population were included (n=1006). They were between 50-66 years old and relatively healthy compared to non-participants. Risk factors included in this project were hypertension, overweight based on the body mass index and waist-hip-ratio, diabetes mellitus, presence of metabolic syndrome, smoking and inflammation level. Brain health risk factors identifiable on MRI include the presence of white matter hyperintensities (WMH) assessed with Fazekas score, a semi-quantitative radiological score, and the presence or not of microhemorrhages (CM).

Of all the risk factors, a significant association were only found between increasing age and load of WMH and the prevalence of cerebral infarction in the HUNT3 MRI-cohort. For more knowledge regarding lifetime risk of cerebral infarction follow-up studies should be done when the data collection from HUNT4 MRI are completed.

1. INTRODUCTION

In Norway stroke is the second most common cause of death. Annually about 11,000 patients are admitted with acute stroke to Norwegian hospitals(1). After a stroke life-long and severe disabilities may occur. Stroke thus poses a major burden on the patients themselves, their relatives, and the health care system. Since the average life expectancy in Norway is steadily increasing, it is estimated that the number of acute strokes also will increase in the future. When planning the future Norwegian health care system data about prevalent diseases such as stroke, collected from the actual Norwegian population, are relevant.

The current medical treatment of stroke is a result of decades of research and scientific progress. A major part of the modern treatment is early intervention in people at risk. Therefore, when working towards preventing and reducing the occurrence of and improve outcome after a stroke, identifying possible risk factors are of great importance. By now, many different risk factors have been identified worldwide, and still the search continues. This study will, thanks to advanced MRI-techniques and a unique Norwegian database, investigate the association between cerebral infarctions on brain MRI and both well-known and potential risk factors of stroke in a general Norwegian population.

Stroke is defined by the World Health Organization as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin”(2). The term stroke includes cerebral infarctions and cerebral hemorrhage. About 85% of all strokes are infarctions(3). Different types of infarctions can cause ischemic damage. Cerebral infarctions are usually caused by reduced blood supply leading to ischemic damage due to a blood clot, either thrombotic or embolic, in an artery or arteriole. In rare cases, ischemia may occur due to a spasm in a vessel or an occluding thickened vessel wall (3). The combination of partially occluded vessels and low blood pressure can also result in ischemic damage and is referred to as watershed infarction. Cerebral hemorrhage is an intracerebral bleeding, which is caused by a rupture of the artery or arteriole (4). Subarachnoid bleeding and extracerebral bleeding are not included in the definition of stroke.

A stroke is a condition that presents with a wide range of clinical symptoms of different severity. The most frequent visible symptoms are paresis in extremities, facial paresis, aphasia, sensitivity disorders, visual impairment or altered level of consciousness (5). The neurological findings and possible disabilities afterwards in the individual patient depend on the extent and location of the injury. For example, the symptoms may be motoric if motor cortex or corticospinal tracts are affected by ischemia or visual impairments may occur due to infarction in the occipital lobe (3). In some cases, the neurological symptoms last for less than 24 hours, and are thus not defined as a stroke. Such short-term neurological symptoms are called transitory ischemic seizures (TIA). Traditionally, TIA was a clinical diagnosis with no visible changes on MRI, but as the technology develops the diagnosis of TIA changed from time-based definition to a tissue-based one. Particularly diffusion weighted imaging-magnetic resonance imaging (DWI-MRI), can detect pathology related to TIA shortly after the onset of symptoms(6).

Infarctions that cause tissue-damage detectable with neuroimaging, but not clinical symptoms are called silent infarctions. In these cases, the patients themselves are not aware that they have a cerebral infarction, because the infarction is asymptomatic, or the symptoms are very mild and short-lived and not considered serious by the patient or attributed to a cerebral event. Silent infarcts are often detected randomly on a computer tomography (CT) or magnetic resonance tomographic imaging (MRI) of the brain(7). In the age group under 65 years, silent infarctions occurred more frequently than clinical infarctions in a Norwegian population(7). TIA and silent infarctions are considered to be associated with an increased risk of clinical infarctions later in life (8). In one systematic review the risk of a subsequent stroke was more than doubled with the presence of a silent infarction (9). When assessing the risk factors of silent infarction, a major overlap with risk factors associated with clinical stroke is observed. Accordingly, some studies, suggest that silent cerebral infarctions may be the preclinical stage of clinically overt strokes(10). The risk profile to both clinical and silent infarctions will be studied in this thesis.

Stroke is a heterogeneous and multifactorial disease with a wide range of different risk factors. For decades, research has identified several risk factors for cerebrovascular disease and stroke, and new risk factors are still being uncovered. In literature, risk factors are

commonly divided into modifiable and non-modifiable risk factors(11). Non-modifiable include age and gender. The modifiable risk factors are associated with lifestyle. Modifiable risk factors are, among others, hypertension, smoking, overweight, diabetes mellitus, and having metabolic syndrome (11). The factors above are established as well-known risk factors. In recent years, less traditional factors such as low inflammation states have been associated with increased stroke risk (12). The mapping of this and other new risk factors are still in progress. One of the larger case-control studies on modifiable and non-modifiable risk factors for stroke is called the INTERSTROKE study(13). The study has a cross-sectional design and over 25,000 cases collected from 32 countries. In the INTERSTROKE study a positive association between cerebral infarction and all the potential risk factors above were found. The HUNT-study provides data on all the risk factors mentioned above in a general Norwegian population.

Factors associated with increased risk of stroke can also be identifiable with neuroimaging. Stroke is usually diagnosed radiologically using CT or MRI. The accessibility and use of MRI-scanning in research and clinical practice has increased rapidly over the last couple of years. Improved technology has increased the sensitivity and specificity in diagnosing both clinical and silent cerebral infarctions. Furthermore, not only findings of infractions can be diagnosed using MRI-scanning. Several changes that are associated with an increased risk of stroke are visible on neuroimaging. In this thesis the particular emphasis will be placed upon the following risk factors: white substance hyperintensities (WMH) and cerebral microhemorrhages (CM).

WMH of presumed vascular origin, earlier known as leukoaraiosis, are a very common finding on magnetic resonance imaging (MRI) or computed tomography (CT) in older adults. WMH are hyperintense, well-defined lesions in the white matter seen on brain T2-weighted FLAIR (fluid-attenuated inversion recovery) scans (see image 2)(14). Some studies associate WMH with a triple the risk of stroke, cognitive impairment and double the risk of dementia(15). Other studies have more divergent results, and more research are needed.

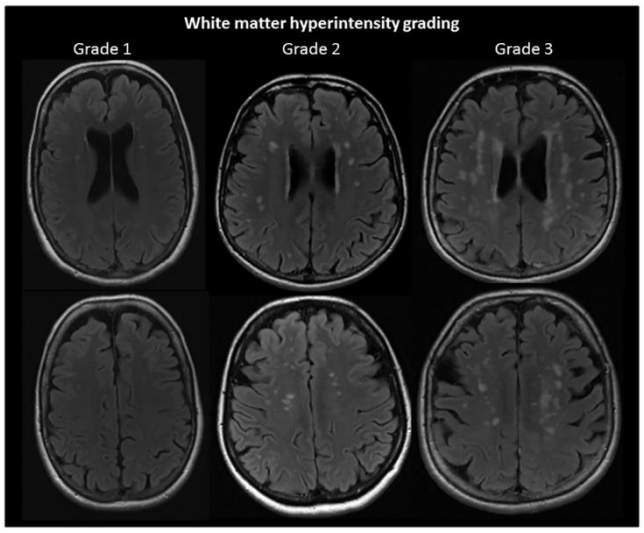

Figure2: Illustration of different load of WMH, graded by the Fazekas scale. The imaging technique used are MRI FLAIR-sequences(7).

CM are another sign of cerebrovascular disease detectable with MRI-scanning. Microhemorrhages can be seen as small foci of signal loss and are presumably related to a circumscribed rupture of small vessels. According to the study named "Cerebral Microhemorrhages: Significance, Associations, Diagnosis, and Treatment", several research studies have demonstrated that these may be used to better estimate the balance between hemorrhagic and cerebral infarctions risks(16). Furthermore, a recent meta-analysis including studies of patients with a previous cerebral infarction or transient ischemic attack (TIA) found that the presence of CM appeared to be an independent marker of recurrent ischemic events in addition to first-ever intracerebral hemorrhage (16). In this thesis, CM will be registered as present or not and the total number of CM.

The aim of this thesis is to investigate modifiable and non-modifiable risk factors of stroke, a selection of both clinical factors and some identifiable with neuroimaging, in a general population. This study will examine the presence of known risk factors for all clinical and silent cerebral infarctions in HUNT3 MRI.

2. MATERIAL AND METHOD

The study was approved by the HUNT study board of directors and the Helse Midt-Norge regional ethics and health research committee, REK midt (2020/322437). The study is approved by HUNT (2021/60234). All participants were adults and legally competent and gave their informed written consent.

The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Movement Sciences, NTNU – Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. The HUNT-MRI was funded by the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology, and the Norwegian National Advisory Unit for functional MRI. The funding sources had no involvement in the study design, data collection, analysis, and interpretation of data; writing of the manuscript; or the decision to submit the manuscript for publication.

2.1 Material:

The data is from the HUNT MRI study, a part of the health surveys in Nord-Trøndelag (HUNT), Norway's largest collection of health information about a general population (17). The project started in 1984 with HUNT 1, and through four rounds has collected health information from about 150,000 participants. The four projects to date are HUNT 1 (1984-1986), HUNT 2 (1995-1997), HUNT 3 (2006-2008) and HUNT 4 (2017-2019). The participants provided a wide selection of data; clinical measurements, blood samples and they completed various questionnaires. In 2008 the HUNT 3 MRI project was initiated, and cerebral MRI was completed in 1006 middle-aged (50-66 year) participants (18).

The HUNT3 MRI-study (n=1006), was an additional project in HUNT3, which is a longitudinal prospective follow up study. It separates from previous studies in being performed on a general population determined by geographical area. The original plan for this medical student thesis was to also include results from HUNT4 MRI, this turned out not to be feasible as HUNT4 MRI is more than 2 years delayed due to the COVID19 pandemic.

2.2 Method

2.2.1 Selection

In the HUNT3 MRI-study the goal was to include 1000 subjects who had participated in HUNT1, 2 and 3 and was between 50–66 years, with an equal sex and age distribution across the age range (see figure 3 for flow diagram). For practical reasons an additional inclusion criterion was living within 45 minutes driving distance from Levanger Hospital, where the MRI-scanning was performed. The exclusion criteria were general MRI contraindications, including weight above 150 kg.

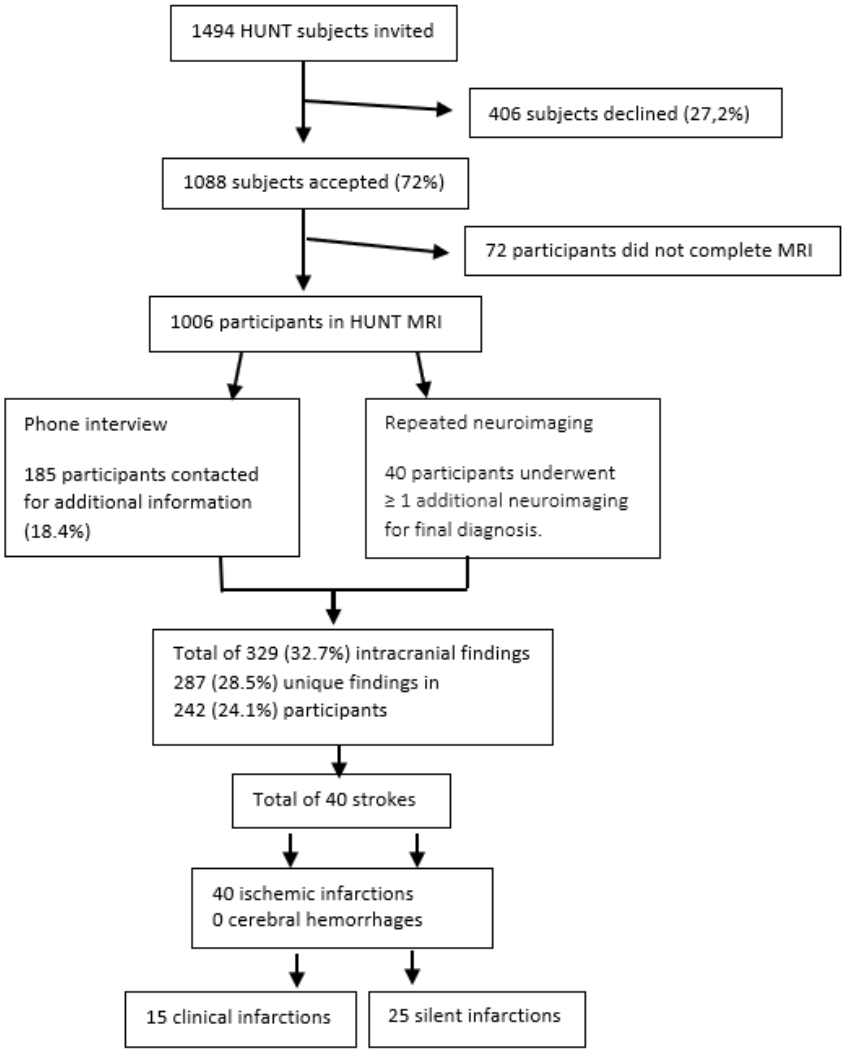

Figure 3. Flow diagram and overview of inclusion and exclusion of participants in the HUNT3 MRI-study, the types and prevalence of classes of strokes. There were 40 incidents of cerebral infarctions among the 1006 participants, this makes the prevalence ≈4%

2.2.2 MRI scan protocol and assessment

The MRI exanimations in HUNT3 were performed between 2007 and 2009. Each examination takes ~50 minutes for each participant. All imaging was performed on the same 1.5 T General Electric Signa HDx 1.5 T MRI scanner equipped with an eight-channel head coil (GE Healthcare) and software version pre14.0M4. MRI protocol included among others a sagittal T1 weighted IR-FSPGR volume, axial T2-, T2-weighted and FLAIR sequences obtained parallel to the anteriorposterior commissure line. All volunteers underwent the same scan protocol, and the examinations were conducted by MRI technologists following a standardized and written procedure. In this study the t-sagittal T1 weighted IR-FSPGR volume, axial T2- weighted FLAIR and T2* scans were used (see **table 1** for scan parameters).

Table 1. Scan parameters for the different sequences in HUNT MRI.

MRI sequence	Matrix size	NSA	TR (ms)	Flip-angle	Slice thickness	Gap	Overlap	FOV
IR-FSPGR	192x192	1	10.2	10°	1.2	0	0	240
T2W	512x320	2	7840.0	90°	4.0	1	0	230
T2*W	256x192	1	500.0	20°	4.0	1	0	230
FLAIR	256x224	1	11,002.0	90°	4.0	1	0	230

Table 1. All imaging was performed on the same 1.5 T General Electric Signa HDx 1.5 T magnetic resonance imaging (MRI) scanner equipped with an eight channel head coil and software version pre-14.0M4(7).

In HUNT3 MRI and HUNT4 MRI all images were assessed independently by two experienced senior neuroradiologists. When assessing the images, they used a standard clinical digital picture archiving and communications system. Apart from the participant's name, birth and examination date, the radiologists were blinded to all previous medical history and previous findings on MRI when first reading the images. Only after describing a finding, they gained access to all earlier radiological examinations and patient records. After working through all images separately, the images were assessed jointly and consensus about difficult cases was reached after discussion. After this, the findings were registered and described using standard neuroradiological procedures.

2.2.3 Classification of findings on MRI

The infarctions were subclassified into silent and clinical infarctions. To determine whether an infarction was clinical or not, the patient records were cross-checked, and interviews conducted over the phone. By thoroughly subclassifying the infarctions it will be possible to compare risk profiles between patients with silent and clinical infarctions.

When assessing WMHs the semi-quantitative Fazekas scale were used. The Fazekas scale rates periventricular and deep WMH combined in a 0–3-point scale depending on the size and confluence of the lesions(19). A score of 3 signifies both larger, more numerous and more confluent lesions than a score of 0 (see figure 2 for illustration). Based on previous studies, a score of 0 or 1 were classified as normal (in a population aged 50-66 years) and a grade of 2 or 3 were considered to be excessive (in a population aged 50-66 years)(20). CM were registered as present or not and the total number of microhemorrhages counted.

To describe the total burden of WMH the semi-quantitative Fazekas score were used. The CM identified on MRI were counted manually and registered by two different radiologists.

*2.2.*4 Defining variables

2.2.4.1 Overview of selected variables

Table 2. Overview of selected variables.

Variable	Definition
MR-variables	
Clinical and silent infarctions	Registered as present
White matter hyperintensities	Measured with Fazekas scale
Microhemorrhages	Registered as present and by quantity
Clinical measurements	
Blood pressure	Mean systolic pressure (mmHg)
Weight	Body Mass Index (BMI)
Body fat distribution	Waist-hip-ratio (WHR)
Smoking	Number of pack-years
Diabetes mellitus/prediabetes	Previously diagnosed diabetes

Metabolic syndrome	A co-occurrence of different risk factors; hypertension, overweight, hypercholesterolemia, hyperglycemia and hyperlipidemia
Blood samples	
C-reactive protein (CRP)	In mg/L
Triglycerides	In mmol/L
Total cholesterol	In mmol/L
Non-fasting glucose	In mmol/L
Questionnaire	
Level of education	Number of years

Table 2. Overview of all the selected variables included in this analysis. All data is collected in the HUNT3 and the HUNT3 MRI-study. All variables described individually below.

2.2.4.2 Clinical variables

Blood pressure

The measured systolic blood pressure was used to identify hypertension. In HUNT3 the blood pressure (BP) measurements followed standardized procedure and were managed by trained nurses. After having rested for at least 5 minutes, the participants BP was measured on the upper arm three times in a sitting position, with one minute between each measurement. The average of the second and third reading was calculated and used for analysis.

Body weight

Weight was measured in kilograms. Overweight is defined as abnormal or excessive fat accumulation that presents a risk to health(21). It is commonly classified using Body Mass Index (BMI) or hip-waist-ratio (HWR). BMI is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2) (who). A BMI greater than or equal to 25 is defined as overweight. Hip-waist-ratio are calculated by dividing the hip circumference on the waist circumference, after measuring according to a standardized protocol (who pdf). According to WHO, to avoid metabolic and cardiovascular complications the WHR should be under 85 for women and under 90 for men. Analysis using both BMI and WHR in the group with and without stroke has been done in this thesis.

Diabetes mellitus

For the analysis in this study either self-reported diagnosed diabetes mellitus serum glucose level above ≥11,1 mmol/L (≥200 mg/dL) will be considered as preexisting or undiagnosed diabetes mellitus or prediabetes. Prediabetes is a condition where blood sugar levels are elevated, but not yet meets the diagnostic criteria for diabetes mellitus.

Metabolic syndrome

The term metabolic syndrome (MetS) refers to the co-occurrence of interconnected risk factors for both stroke and cardiovascular disease. In the literature multiple definitions of MetS are found, but the American Heart Association recommended a common definition of MetS based upon the presence of any 3 of the following 5 risk factors: insulin resistance, high cholesterol levels, high triglycerides levels, abdominal obesity and hypertension (See table 3 for more details about measurements and cut-off-values recommended)(22). Due to limitation in the collected data in HUNT 3, some changes from the recommended definition had to be made in measurements and cut-off values. The changes were: for measuring insulin resistance, a random non fasting blood glucose measurement was used instead of fasting glucose, for cholesterol levels total cholesterol instead of high-density lipoprotein cholesterol (HDL-C were collected in HUNT3, but not used), for triglycerides the self-reported question regarding treatment were not available and waist-hip-ratio was used instead of hip circumference (see table 4 for more details and cut off values used in this analysis.)

Table 3. Standard measurements and cut-off values for metabolic syndrome

Clinical finding	Measurement	Cut-off values
Hypertension	Systolic blood pressure	SBP ≥130 mmHg
	Diastolic blood pressure	DBP ≥ 85 mmHg
	Undergoing drug treatment for hypertension	Self-reported
Abdominal obesity	Waist circumference	> 102 cm in males > 88 cm in females**
Insulin resistance	Fasting blood glucose	FPG ≥100 mg/dL

	Undergoing treatment for diabetes mellitus	Self-reported
Cholesterol levels	HDL-C	<40 mg/dL in males <50 mg/dL in females
	Undergoing drug treatment for reduced cholesterol	Self-reported
Triglycerides	Triglycerides (TG)	≥150 mg/dL
	Undergoing drug treatment for elevated triglycerides	Self-reported

Table 3. Metabolic syndrome as recommended by the American heart association and proposed as a way to standardize metabolic syndrome in research. ** for people of most ancestries living in the United States. Ethnicity- and country-specific thresholds can be used for diagnosis in other groups, particularly Asians and individuals of non-European ancestry who have predominantly resided outside the United States.

Table 4. Adjusted measurements and cut-off values used in this analysis.

Clinical finding	Measurement	Cut-off values
Hypertension	Systolic blood pressure	SBP ≥140 mm Hg
	Undergoing drug treatment for hypertension	Self-reported
Abdominal obesity	Waist-hip-ratio	>0.90 in men >0.85cm in women
Insulin resistance	Random blood glucose	≥11.1 mmol/L
	Undergoing treatment for diabetes mellitus	Self-reported
Cholesterol levels	Total cholesterol	≥ 7.8 mmol/L
	Undergoing drug treatment for reduced cholesterol	Self-reported
Triglycerides	Triglycerides (TG)	≥1.7 mmol/L

Table 4. Overview of measurements and cut-off values used in this thesis adjusted to the data available in the HUNT3-study. Changes in the measurements of abdominal obesity, insulin resistance, triglycerides (self-reported drug treatment not available) and cholesterol levels were made.

Smoking

Smoking was based on pack-years (PY). PY are an internationally standardized measure for cumulative smoking dosage during a lifetime. Based upon self-reported data from the questionnaire the number of smoking pack-years per participant was calculated. One pack-year equals 20 cigarettes per day for a year(23). To determine a patient's pack-year (PY)

history information on the average number of packages (one package equals 20 cigarettes) smoked daily (N) and the number of years smoking. The formula is N x T = PY(24).

C-reactive protein

Elevated C-reactive protein is measured in blood serum. A value >5 mmol/L is considered the cut-off for clinical ongoing inflammation(25). Slightly elevated values between 0-5 mmol/L can be an indication of an ongoing low-inflammatory state(12).

2.2.5 Statistical analyses

All data analysis was performed in IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Results are given as percentage with 95% CI where appropriate and as mean ± standard deviation for group data. The statistical significance was set to $p < 0.05$, two-tailed. All 40 participants (men and women) with a cerebral infarction (silent and clinical) were analyzed as one group.

In this thesis the link between cerebral infarction and different risk factors were evaluated by implementing three different statistical analyses. First, differences in the frequency of a risk factor on having a cerebral infarction or not was investigated with a Chi-square and Fisher's exact test. This analysis was performed on the following risk factor groups: man-woman, low-high education, normal-excessive load of WMH, having-not having cerebral microhemorrhages, normotensive-hypertensive, normal weight-overweight, not having-having diabetes mellitus, not having-having metabolic syndrome, non-smokers-smokers and normal-elevated hs-CRP. Secondly, unpaired t-tests were used to test for differences in the risk factors as continuous measures between the group of participants with infarctions the group of infarction-free participants. The continuous variables tested were age, blood pressure, body mass index, waist-hip-ratio in men, waist-hip-ratio in women, smoking pack-years and C-reactive protein. Lastly, binary logic regression was used to assess the odd ratio of a selection of risk factors for presence of a cerebral infarction. The selected risk factors were age, load of white matter hyperintensities, blood pressure, Body Mass Index, smoking pack-years and C-reactive protein. All variables were included as continuous scales, except load of white matter hyperintensities who were categorical (normal-excessive).

3 Results

3.1 Principal findings

Only increasing age and load of WMH had a significant link to cerebral infarction in our analyses. No other variables had a significant link to cerebral infarctions. More information regarding each variable individually follows below.

In the HUNT3 MRI-cohort, age was significantly higher amongst the participants with cerebral infarction compared to those without (mean difference of 1.6 years). In the binary logic regression model, no association between age and cerebral infarction was found. However, an association between excessive load of WMH and cerebral infarction was present. When comparing the group with excessive WMH to those with normal load of WMH no significant difference in prevalence of infarctions were found. Because both prevalence of cerebral infarction and load of WMH are known to be strongly related to increasing age, it is possible that age was a confounder in the binary logic regression model.

3.2 Population

In the HUNT3 MRI-cohort 1006 participants from a general population were included (see table 5 below for an overview of the HUNT3 MRI-cohort). Among them it was 40 participants who had a cerebral infarction identifiable on MRI. Out of the 40 cerebral infarctions 16 were clinical and 24 were silent. Clinical and silent cerebral infarctions were analyzed as one group in this thesis, as the number of infarctions were considered too low for further subclassification. Table 5 provides an overview of demographic and health characteristics of those with and without cerebral infarction.

Table 5. Overview of the HUNT3 MRI-cohort and comparisons between subgroups

	Total	Women	Men	Age	SBP	BMI	Fazekas score
Total MRI-cohort	1006	530	476	59.0	131	26.9	0.58
Without infarction	966	514	452	58.9	131	26.9	0.58
With infarction	40	16	24	60.5	132	27.0	0.78

Silent infarction	25	9	16	59.9	132	26.9	0.67
Clinical infarction	15	9	6	62.6	133	27.5	1.0

Table 5. An overview of the total HUNT3 MRI-cohort. Subclassified according to sex, presence of infarction (present or not) and type of infarction (clinical or silent). A significant link between age and Fazekas score to cerebral infarctions were found in this thesis (table 7, table 8).

3.3 Statistical analyses

Three different analyses were implemented in this thesis. The different analysis where Chi-square and Fischer exact test (see table 6 for results), T-test (see table 7 for results) and a binary logic regression model (see table 8 for results).

Table 6. Results of the Chi-square and Fisher's exact test

Variable	Participants Included (n=1006)	Participants with values above cut-off	Infarctions in group with values above cut-off	Exact Sig. (2-sided)
Sex	1006	530	16	0.11
Education	869	241	8	0.85
White matter hyperintensities	953	88	7	0.41
Microhemorrhages	1006	41	1	1.00
Systolic blood pressure	995	401	12	0.86
Body Mass Index	993	683	28	0.73
Waist-hip-ratio (men)	476	282	18	0.10
Waist-hip-ratio (women)	530	324	14	0.77
Diabetes mellitus/Prediabetes	948	37	2	0.66
Metabolic syndrome	923	243	13	0.26
Smoking	941	532	13	0.43
C-reactive protein	969	555	18	0.56

Table 6. Results: No significant difference between groups in any of the variables. **Cut-off values** for all the variables: **Sex**: women. **Education:** >3 years at college level. **WMH:** Abnormal Fazekas score= >1. **Cerebral microhemorrhages:** Present or not. **Systolic blood pressure:** ≥ 140 mmHg and/or self-reported current antihypertensive treatment. **Body Mass Index:** >25. **Waist-hip-ratio (men):** >0.90. **Waist-hip-ratio (women):** >0.85. **Diabetes mellitus/prediabetes:** Self-reported

diabetes mellitus or non-fasting glucose level >11.0 mmol/L. **Metabolic syndrome:** ≥ 3 positive variables. **Smoking:** Self-reported regular smoking. **C-reactive protein:** >1 mg/L.

Table 7. Results of the T-tests

Variable	Sig.	CI Low	CI High
Age	0.14	1.03	1.28
White matter hyperintensities	0.001	0.10	0.56
Systolic blood pressure	0.65	0.97	1.02
BMI	0.85	0.06	518.92
Smoking pack-years	0.88	0.96	1.03
C-reactive protein	0.46	0.77	1.12

Table 7. Result: The participants with stroke were significantly older than the participants without stroke. Age was the only variable with a significant link to cerebral infarction when we analyzed the variables as continuous scales. **WHR:** Men and women were analyzed separately due to physiological differences in fat distribution between the sexes.

Table 8. Results of the Binary logic regression model

Variable	Participants	Infarctions	Sig. (2-tailed)	CI Low	CI High
Age	1006	40	0.004	-3.29	-6.67
Systolic blood pressure	993	38	0.94	-5.32	5.68
Body Mass Index	954	39	0.86	-1.29	1.07
Waist-hip-ratio (men)	476	24	0.35	-0.03	0.02
Waist-hip-ratio (women)	530	16	0.43	-0.12	0.08
Smoking pack-years	914	27	0.94	-4.56	4.20
C-reactive protein	941	28	0.49	-1.12	2.47

Table 8. Result: An association between only excessive load of WMH and cerebral infarction were observed. We found no association to age in the binary logic regression model, despite that age was significantly higher among the participants with infarction compared to those without in the t-test (table 7). **Variables:** WMH was included as a categorical variable (excessive/normal). All other variables were included as continuous scales. **Missing cases**: 929 participants included (26 infarctions) equals 7.6% missing cases.

Age

The participants with cerebral infarction had a significantly higher age, than the participants without infarction (table 6). In the binary logic regression model, we found no association between age and cerebral infarction However, we did find an association between cerebral infarction and load of WMH, which is a phenomenon strongly related to increasing age (table 8).

White matter hyperintensities

When comparing the group with excessive WMH (n=88) to the group with normal load of WMH we found no significant difference in prevalence of cerebral infarctions (see table 6). WHR were included in the binary logic regression model as a categorical variable (excessive/normal). The model showed a significant association between excessive load of WMH and cerebral infarctions.

Cerebral microhemorrhage

It was no significant difference in the group with CM (n=41) and the group without, regarding incidents of cerebral infarctions (table 6). The prevalence of CM (1.3%) in the HUNT3 MRI-cohort were much lower compared to similar cohorts in a general population.

Blood pressure

The group with systolic blood pressure ≥ 140 mmHg and/or undergoing self-reported current medical treatment for hypertension (n=401) had no higher prevalence of cerebral infarctions than the group with systolic blood pressure <140 mmHg (table 6). Between the groups with and without infarction it was no significant difference in blood pressure when analyzing blood pressure as a continuous scale (table 7). Blood pressure was included in the binary logic regression model as a continuous scale. The model showed no association between blood pressure and cerebral infarctions (table 8).

Weight and fat distribution

Both BMI and WHR were investigated in this thesis. The group with BMI >25 (n=683) had no significantly higher prevalence of cerebral infarction than the group with BMI <25 (table 6). The participants with infarction had no significantly higher BMI than the group without stroke (table 7). BMI were included in the binary logic regression model. No association between BMI and cerebral infarction were found (table 8).

WHR were analyzed separately for men and women, due to different cut-off values in the sexes. In men, the groups with WHR >0.9 (n=282) and <0.9 had no difference in prevalence of cerebral infarction (table 6). In women, the group with WHR >0.85 (n=324) had no higher prevalence of cerebral infarctions compared to the group with WHR <0.85. In the groups with and without stroke we found no significant difference in WHR when analyzing it as a continuous scale, in neither men nor women (table 7).

Diabetes mellitus and prediabetes

The participants with self-reported diabetes mellitus and those with a non-fasting glucose level above >11.0 mmol/L were registered in one group as diabetics and prediabetics (n=37). This group had no significantly higher prevalence of cerebral infarctions than the rest of the HUNT3-MRI cohort (table 6).

Metabolic syndrome

The group (n=243) with metabolic syndrome (see table XX for overview of criteria), had no significantly higher prevalence of cerebral infarction than the group without the syndrome (table 6).

Smoking

It was no significantly higher prevalence of cerebral infarctions among the participants who reported to be current or previous smokers (n=532) compared to the non-smokers (table 6).

When analyzing the number of pack-years as a continuous scale, we found no significant difference between the participants with and without infarction (table 7). Pack-years were included in the binary logic regression model as a continuous scale. It was no association between pack-years and cerebral infarction in the model (table 8).

C-reactive protein

The prevalence of cerebral infarction was not significantly higher in the group with hs-CRP >1 (n=555) compared to the rest of the HUNT3 MRI-cohort (table 6). When comparing the participants with and without stroke we found no significant difference in CRP-level (table 7). CRP were included in the binary regression model as a continuous variable. The model showed to association between cerebral infarctions and CRP-level (table 8).

4. Discussion

4.1 Principal findings

Consistent with previous studies, we found that age was an important risk factor for cerebral infarction in a general population(8). Besides increasing age and higher load of WMH, none of the selected variables in this study proved to have a significant link to increased risk of cerebral infarction. This was despite that all variables (see table 2 for an overview of all variables included) were found to be risk factors for cerebral infarctions in other large studies(13). All risk factors included in this thesis are discussed individually below.

In multiple ways, this cross-sectional observational study of a general population (n=1006) separates from other large studies on risk factors for cerebral infarction. We are investigating a general population and not a hospital based one. Clinical and silent infarctions detectable on MRI were analyzed as one group in this thesis, as the number of infarctions (n=40) were considered too low for further subclassification.

Some limitations in this thesis are, among others, the relatively young (age 50 -66 years) of the HUNT3 MRI-cohort. This is an age group with overall low incidence rate of both clinical and silent cerebral infarctions. Possibly, some connections between risk factors and cerebral

infarctions are only visible on a populational level and the HUNT3 MRI-cohort are too small. The number of participants were 1006 and only 40 participants had a cerebral infarction. Furthermore, the HUNT3 MRI-cohort were healthier and had a better cardiovascular risk profile compared to the general population (compared to ≈12000 non-participants)(26).

The HUNT3 MRI-cohort had a somewhat better cardiovascular risk profile, compared to participants from the HUNT3-study who were eligible but not invited to the MRI-study (n=12473)(26). In comparison to the non-participants, our cohort had a lower blood pressure, lower cholesterol and obesity was less prevalent. Their education level was slightly higher, and they were somewhat younger than the non-participants. As a result of this, Honningsvåg et al. conclude that the participants can have somewhat less brain morphological changes related to cardiovascular risk factors than the general population.

4.2 Discussion of variables

Age

Age was a significant risk factor for cerebral infarction in the HUNT3 MR-cohort. In the cohort the age range was from 50 to 66 years old. Out of all strokes in Norway only 8.1% occur in adults <55 years. Indeed, in Norway the average age of a first stroke incident (includes both cerebral infarctions and hemorrhage) is 74 years (77 years for women and 72 for men)(27) This is almost 10 years older than the oldest participants in the HUNT3 MR-cohort. Nevertheless, even in this group with low risk of infarction due to their relatively young age, we found a significant effect of age on presence of an infarction on MRI. The participants with infarction were on average 60.5 ± 4.3 years old and those without stroke were 58.9 ± 4.2 years. The age of our participants must be taken into account when interpreting the results, as the participants in large studies regarding cerebral infarctions tend to be older(13).

Age is a non-modifiable risk factor, and unfortunately not possible to change directly. Indirectly some of the detrimental effects of increasing age may be modifiable, if we can identify what makes older people more prone to cerebral infarctions.

Comorbidity is one challenge when trying to prevent cerebral infarctions in an increasingly older population. In Norway, the prevalence of lifestyle related diseases and other chronic diseases increases with age. Older adults are therefore more likely to have several diseases such as hypertension and diabetes mellitus(28). Diagnoses that are both established as risk factors for cerebral infarctions(29). Furthermore, studies have shown that the longer the duration of conditions such as hypertension and diabetes mellitus, the bigger the risk of cerebral infarction(30). Resulting in both a higher prevalence of diseases associated with increased risk of cerebral infarctions and more severe negative side-effects of these conditions with increasing age. This shows the importance of identifying people at risk of disorders at an early stage and follow up by intervention to reduce the lifetime risk of infarction.

The age range in the HUNT3-MRI is 15 years (from 50 to 66 years old), which arguably can be considered both too low and to narrow when investigating cerebral infarctions. Less than 10% of cerebral infarctions occur in patients <55 years old, and it is therefore very likely that only a small fraction of all the cerebral infarctions that will occur during this cohort's lifespan will be included in this analysis. Therefore, future follow-up studies (as the HUNT-studies enables) are important to be able to uncover the lifetime risk of cerebral infarctions in this cohort.

Age was significantly higher in the group with infarction compared to the infarction-free participants (see table 7). This was despite the relatively young age, narrow age-range and the slightly better health in this cohort (compared to non-participants)(26). For these reasons, the association between increasing age and increased risk of cerebral infarction is considered strong.

White matter hyperintensities

The binary logic regression model showed a significant association between excessive load of WMH and cerebral infarctions. WHR were included in the model as a categorical variable (excessive/normal). However, when comparing the group with excessive WMH (n=88) to the group with normal load of WMH we found no significant difference in prevalence of cerebral

infarctions (see table 6). Age might be a possible confounder, due to its strong association to both load of WMH and increased stroke risk.

In the HUNT MRI cohort excessive WMH were present in ~9%, which is slightly higher than what is reported in other similar cohorts(31). Out of 917 participants 81 had an abnormal Fazekas score. The load of WMHs in this cohort aged 50-66 years was registered as normal (Fazekas score =1) or above normal (Fazekas score >1).

WMH are a common finding on MRI or CT in older adults. The pathophysiology behind how and why WMH develop is still debated(14). In addition to increased risk of cerebral infarctions, studies have found an association between WMH and other age-related illnesses. Examples are cognitive decline (32), decline in physical function (33) and higher cardiovascular mortality (34). WMHs is therefore considered a warning sign of clinical importance and not just an age-related phenomenon.

WMH can be described using semi-quantitative rating scales and by volumetric measures. Clinically, WMH are often described using the Fazekas scale. Volumetric measures of total WMH burden can be obtained manually and (semi-) automatically. The gold standard is considered manual delineation. For prospective follow-up studies, whereas the development of WMH over time is of interest, volumetric measures are more detailed and often chosen. For this cross-sectional observational study, the Fazekas scale were used since we wanted to implement common clinical measures, readily available in the project.

Our results provide some support for WMH being a risk factor for stroke. In our analyses we only found a significant association between excessive WMH and increased stroke risk in the binary linear regression model, and not when comparing the groups with excessive and normal load of WMH separately. For that reason, the load of WMH is most likely not an independent risk factor for cerebral infarction in the HUNT3 MRI-cohort.

This does not exclude that WMH could be of clinical use, as suggested by other studies, when estimating risk of future cerebrovascular events or get an overall impression of brain health. Further analysis and follow-up studies are needed to determine the value of the results in this thesis and explore the clinical utility of WMH further.

Cerebral microhemorrhages

We found no link between the presence of CM and having a cerebral infarction. In HUNT MRI CM occurred only in 1.3% of the participants, which equals 13 participants. Out of these 13 participants only one had a cerebral infarction. Thus, the prevalence of CM were much lower in the HUNT3 MRI-study compared to studies in similar populations (35).

The clinical significance of CM found in a person from a general population is still being debated, but an association with established risk factors for cardiovascular disease, namely hypertension, diabetes mellitus and inflammation is considered likely(36). Multiple recent studies have observed an independent correlation between the presence of any CM and the risk of all strokes. The Rotterdam Study is a cohort study with a 5-years follow up time of 4579 participants aged 45 or more(34). In that study the presence of any CM on baseline MRI multiplied the risk of all strokes by a factor of approximately 2 in age- and sex-adjusted analyses. These results were supported by another meta-analysis in Western (mostly Europeans) participants including patients with a previous cerebral infarction or transient ischemic attack (TIA), which also found that CM appeared to be an independent neuroimaging biomarker for cerebral infarctions(37). Furthermore, several studies have demonstrated that the presence of CM may be used to better estimate the balance between hemorrhagic and ischemic risks(16). A possibility that has evoked great interest as it might be of clinical value for more personalized medicine in the future.

As mentioned above, in studies of other similarly aged and healthy controls, the prevalence of CM is reported to be much higher at ~3–8% (35). This can, among other things, be because the HUNT MRI cohort was in relatively good health. In the study “Incidental Intracranial Findings and Their Clinical Impact” it is suggested that regional and/or population dependent factors are important for the prevalence of microhemorrhages, due

to similarly low prevalence found in other cohorts(31). The results in this thesis might support the theory that suggest that CM are more connected to cerebral hemorrhage than infarctions. This is an interesting theory that requires further investigations in prospective follow-up studies of this cohort. Further research on the correlation between CM and risk of cerebral infarction and the clinical importance of these findings are interesting topics for further research.

Hypertension

No significant relationship between blood pressure and stroke risk was found in this population, even though hypertension is established as an important modifiable risk factor for cerebral infarction. The group with systolic blood pressure ≥ 140 mmHg (n=300) had no higher prevalence of cerebral infarctions than the group with systolic blood pressure <140 mmHg (table 6). Between the groups with and without infarction it was no significant difference in blood pressure when analyzing blood pressure as a continuous scale (table 7). Blood pressure was included in the binary logic regression model as a continuous scale. The model showed no association between blood pressure and cerebral infarctions (table 8).

Hypertension is described as the most important modifiable risk factor for cerebral infarction(13). The association between hypertension and risk of stroke (cerebral infarctions and cerebral hemorrhage) is linear and independent of other risk factors (38). In a Norwegian study (n≈13,000) the risk of stroke increased by 30% per 15 mmHg increase in systolic blood pressure(39). A case-control study from the UK (n=1.25 millions) found that the lifetime risk for cerebral infarction among normotensive patients was 6.5% and among hypertensive patients it was 7.6% (40). This speaks of the importance of preventive action directed towards limiting hypertension to reduce negative long-term consequences of hypertension, such as stroke. Careful assessment and treatment of hypertension, by medication or lifestyle changes, are the most efficient way to reduce the national and global burden of stroke. Calculations suggest that approximately 70-80% of strokes can be prevented by reducing blood pressure with antihypertensive treatment(13).

In the HUNT3 MRI-cohort ≈20% (n=194) reported to be on antihypertensive treatment. Nationally, in the age group from 50 to 64 years old 25% use antihypertensive treatment according to "Reseptregisteret"(41). The 5-percentage difference can be explained by the slightly better general health in the HUNT3 MRI-cohort. There is also some uncertainty regarding the numbers from HUNT3, as they are based on self-report and some participants may have reported incorrectly. As the number of participants on antihypertensive treatment is so high (1/5 of the cohort), one can assume that the blood pressure in this cohort in general is followed-up and treated by physicians. Perhaps can this be some of the explanation to the lower prevalence of cerebral infarctions in this cohort compared to other similar, general populations at approximately the same age.

To investigate the correlation between blood pressure and cerebral infarction different statistical analysis were done in this thesis. In line with previous large studies, like the INTERSTROKE case control study (n=26919) and the "AHA Stroke Risk Factors, Genetics, and Prevention" study, both participants with self-reported current use of antihypertensive treatment and/or measured blood pressure above a cut-off value were registered as hypertensive. The cut-off value for describing hypertension varies from nation to nation and in clinical practice and research. In Norwegian guidelines hypertension is defined as ≥ 140/90 mmHg (with some exceptions)(42). In this thesis a cut-off value of systolic blood pressure ≥ 140 mmHg was selected, to be in line with national guidelines.

In this population (n=997) 300 participants had SBP ≥ 140 mmHg and 192 participants reported to be undergoing medical treatment for hypertension. 91 participants had both SBP ≥140 mmHg and used antihypertensive medications. By selecting a higher cut-off value (as done in other studies), we would have had a smaller group of participants registered with hypertension and more severe hypertension in the group. This might have resulted in a higher average systolic blood pressure in the group with infarctions compared to the group without infarctions. Increasingly high systolic blood pressure has been linked to increasingly elevated risk of cerebral infarction in other studies(13).

Several factors can explain why we do not find any relationship between cerebral infarction risk and hypertension in our population at this point. When performing the chi-square test, both participants with SBP ≥ 140 mmHg and those using antihypertensive drugs were included. This includes 101 participants who were on antihypertensive medication and had a SBP <140 mmHg. Their previously high blood pressure was thus adequately treated, the negative consequences of hypertension such as increased stroke risk might be reduced. This can have led us to the null result. The t-test investigates whether there is difference in the average systolic blood pressure in the group with or without infarctions. One weakness with the t-test is that participants with an infarction (in particular clinical infarction) might have been prescribed antihypertensive treatment as a consequence of their stroke. This might result in participants being registered with SBP <140 mmHg and stroke, regardless of what the blood pressure was before the stroke originally occurred.

That hypertension increases lifetime risk of stroke in a general population has been reported in other studies. Amongst these is a large Japanese cohort study with 5789 randomized participants and a follow-up time of 18 years(43). The conclusion of this study was that in an urban community-based population, the participants with hypertension had a significantly increased lifetime risk of cerebral infarction. It would therefore be of great interest to do a follow-up study when the data collection from HUNT 4 is completed, and thereby see how hypertension will affect risk of cerebral infarction in a mostly rural Norwegian population over time.

Several reasons can explain why we did not find a link between blood pressure or hypertension and presence of cerebral infarction in HUNT3. Just because hypertension was not a significant risk factor in this cohort at one exact point in time, it is still important to do follow-up studies to be able to investigate the lifetime risk of stroke for hypertensive patients.

Body weight

We found no link between increasing body weight (BMI) or distribution of weight (WHR) and cerebral infarction in this thesis. Both BMI and WHR have been included in the Chi-square

and T-tests. Due to different cut off-values in WHR for men and women they were analyzed separately. For the binary logic regression model only BMI was included, as it is the most common clinical measure of the two.

In the literature, both increased BMI and WHR have been found to be associated with increased risk of cerebral infarction, independent of age, lifestyle and other cardiovascular risk factors(8). In the large INTERSTROKE-study abdominal obesity (WHR) was found to have a stronger link to increased stroke risk than increased overall weight (BMI)(13). Therefore, both measures were included in this analysis, to investigate the possible differences between the measurements link to risk of cerebral infarction.

According to WHO, to avoid metabolic and cardiovascular complications the WHR should be <0.85 for women and under <0.90 for men. Out of the 476 men included ≈75% had an WHR above the recommended 0.9. The highest value was 1.17 and only 50 participants had a value above 1.0. Out of the 530 women included ≈60% had an WHR above the recommended 0.85. In both sexes well above half of the participants had a higher WHR than recommended. These numbers indicate that there is several (75% of the men) that have a value slightly above the recommended level, but very few with severe obesity. One reason for this is that a weight above 150 kilograms was an exclusion criterion for the MRI-study, due to weight limitation for the MRI-machine. People with values above the recommended level are prone to the metabolic and cardiovascular complications following abdominal obesity. Despite of this, we found no significant differences when comparing the group with and without infarction.

Increased WHR is more associated with increased risk of infarction in women than in men(44). Compared to the men 15 percentage points less of the women were registered with a WHR above recommended level. This can have been one contributing factor to why we found no significant relationship with increasing WHR and risk of cerebral infarction.

Even though none of the measures proved to have significant link to presence of cerebral infarction in this cohort at this point, it is still out of great interest to compare the two in future follow-up studies to observe possible changes. If future studies find more indications that overweight is an independent risk factor for cerebral infarction, it might be a reason to strengthen weight-loss programs and other treatment options for overweight.

Diabetes mellitus

We found no significant link between diabetes mellitus or prediabetes and presence of cerebral infarction in this study. The participants with self-reported diabetes mellitus and those with a non-fasting glucose level above >11.0 mmol/L were registered in one group as diabetics and prediabetics (n=37). This group had no significantly higher prevalence of cerebral infarctions than the rest of the HUNT3-MRI cohort (table 6).

Over the last decade, an increasing prevalence of diabetes mellitus has been observed worldwide. Norway is no exception, and per 2020 about 5% of the Norwegian population had a diagnosis of diabetes mellitus(45). In the United States the prevalence of diabetes was approximately 8% and nearly half of Americans ≥65 years of age are considered prediabetic(46). Since prediabetics also have increased risk of stroke, this group were included in our analysis(30). Out of 948 participants in this study, 37 were registered as having diabetes mellitus or a random glucose level above 11,1 mmol/L. This equals 3.7% of the population, which is 1.3% percentage points below the national level. It can be that the prevalence of diabetes (prediabetes) in this cohort was a bit lower due to the relatively younger age and good health of the participants.

American studies point to the “epidemic” of diabetes as a significance risk for cerebral infarction(47). One study estimated that 37-42% of all strokes are attributable to the effects of diabetes alone or in combination with hypertension. This estimate is quite high compared to other studies, where the magnitude of risk varies(48). Nevertheless, the effect is significant and it is especially notable in the age of the HUNT3 cohort participants.

That (pre-)diabetes is a risk factor significant in an American cohort younger than 66 years old but not in the HUNT3 MRI-cohort can have many possible explanations. We are examining a relatively small cohort (n=948) with a much lower prevalence of diabetic and pre-diabetic participants than found in the American studies. Perhaps, the interaction between diabetes mellitus and increased risk of cerebral infarction is only present at a population level. With only 1.3% of the HUNT population stratified to the diabetes/prediabetes group, it is portably not possible to uncover similar findings as in populations with much higher prevenances. Also, the negative consequences of diabetes and hypertension could be greater in the United States due to differences between the American and Norwegian health care systems. Patients may be treated better in the Norwegian health care system and therefore be less vulnerable to the negative side-effects of their disease.

The Northern Manhattan Study found that the duration of diabetes mellitus was associated with cerebral infarction. The adjusted hazard ratio was increasing 1.03 per year with diabetes mellitus and after ≥10 years it was observed a markedly increase in stroke risk(30). A weakness of our study is that it did not take into consideration the duration of the diabetes/prediabetes. Other factors that could be considered for future studies are the types of treatment used and how well the blood sugar is regulated, which are factors proven to affect stroke risk in other studies. As the prevalence of diabetes mellitus is increasing in the Norwegian population, knowledge on how to treat and reduce the risk of diabetes and its comorbidity on brain health is in the patients´ and the health-care system´s best interest.

Metabolic syndrome

We found no link between higher metabolic score or having metabolic syndrome and presence of cerebral infarction in this cohort. Due to alterations from the standardized measures in metabolic syndrome, the results in this thesis must be interpreted as an indication as it does not represent the standardized metabolic syndrome.

Metabolic syndrome (MetS) is a complex disorder defined by a cluster of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases and stroke. The combination of hypertension, abdominal obesity, insulin resistance, elevated cholesterol and elevated triglyceride has proven to collectively increase the risk of stroke(13). Having metabolic syndrome is defined by the presence of any 3 of the 5 risk factors mentioned above (see table 4 for an overview). The conditions are interrelated and share underlying mediators, mechanisms, and pathways.

For this thesis the metabolic syndrome measurements were adjusted from the internationally recommended standard due to limitations in the available HUNT-data. For instance, for measuring insulin resistance, a random non fasting blood glucose measurement was used instead of fasting glucose and for cholesterol levels total cholesterol instead of High-density lipoprotein cholesterol (HDL-C were collected in HUNT3, but not used). Waist-hip-ratio was used instead of hip circumference. The cut-off values for the waist-hip-ratio, non-fasting blood glucose and the total cholesterol were similar to what is considered pathological or the threshold for medical intervention in Norwegian guidelines(49,50)

In this cohort, it did not make any difference to investigate the risk factors combined as metabolic syndrome. Neither when investigating the risk factors individually nor collectively, did we find a connection to presence of cerebral infarction on MRI.

Smoking

No significant relation was found between cigarette smoking or PY and stroke in this population, neither by comparing participants who currently was or had been smokers to those who had never smoked, nor by investigating the relation between cumulative smoking dosage as pack-years and stroke frequency.

In the HUNT3 MRI-cohort 581 participants claimed to be previous or current smokers. 234 participants (23% of the cohort) claimed to be current smokers. Out of the current smokers 156 (15%) reported to smoke daily and 78 (8%) reported to smoke occasionally. According to a report from Folkehelseinstituttet (2017), approximately 10% of the Norwegian population in the age group from 50-66 years old were current daily smokers(23). Compared to the general Norwegian population, it was a higher prevalence of daily smokers in the HUNT3 MRI-cohort.

In literature cigarette smoking has long been established as a well-known risk factor for cardiovascular disease, and the association between smoking and cerebral infarction has been found in more recent years (51,52). A large meta-analysis from 1989 found that cigarette smoking nearly doubled the risk with a dose–response relationship between pack-years and stroke risk(51).

In our results we found no link between the number of PY and presence of stroke by using a t-test or in the binary logistic regression model. Among the smokers the average number of PYs were approximately 15 PY and it were 107 participants who had smoked 25 PY or more. Thus, approximately 10% of the total HUNT3 MRI-cohort had smoked 25 PY or more during their lifetime.

It could be several reasons why we did not find the same differences as in other studies when comparing smokers to non-smokers in this cohort. An average on 15 PY per person can be a too low cumulative dosage to significantly increase the risk of cerebral infarction. The number of participants (n=1006) could be too small to see the effect of smoking on risk of cerebral infarction. As the number PY are calculated based on self-reported data it may be underreported and possibly contribute to a lower-than-normal link between smokers and risk of cerebral infarction. Furthermore, 60% of all the smokers claimed to have quit. This may affect the results as two large studies suggest that smoking cessation rapidly reduces the risk of stroke, with excess risk nearly disappearing 2 to 4 years after smoking cessation(51).

For the chi-square test all participants reporting to be previous or current smokers were analyzed as one group and compared to those who claimed never to have smoked. The weakness of this design is, among other things, that the cumulative smoking dosage was not considered. Furthermore, it does not take into account that many regular smokers had quit or reduced their consumption. As mentioned above smoking cessation rapidly reduced stroke risk. An effect that could have interfered with our results.

The results may indicate that smoking cessation rapidly reduces the increased risk of cerebral infarction linked to cigarette smoking, that the increased risk is more prominent in older cohorts and/or that a cumulative smoking dosage needs to be higher than >25 PY for having a significant impact on the risk of future cerebral infarction. In the literature, smoking is known to be a risk factor for cerebral infarctions and other severe diseases and we strongly advice not to smoke, regardless of the findings in this thesis.

C-reactive protein

No significant relation between elevated baseline CRP and presence of cerebral infarction were found in this thesis, neither by comparing the groups with and without elevated CRP nor by analyzing elevated CRP-level as a continuous scale.

In recent years, low-grade elevation of CRP in serum has been found to independently predict cardiovascular disease (CVD) and elevated risk for cerebral infarction (12). A CRP level >5 mg/L is considered the cut-off value for inflammation clinically and values <5 mg/l is considered a possible low-inflammatory state. In more recent years, high sensitivity CRP (hs-CRP) has been developed and the use of this method is increasing especially in research. Hs-CRP has improved sensitivity and allows us to measure CRP levels accurately down to around 0.3 mg/L. Hs-CRP is used in the HUNT3-study.

Out of 971 participants 935 had a CRP between 0,1 and 5,0 mg/L. 481 participants had a value between 1.0 and 5.0 mg/L. One meta-analysis named "Hs-CRP in stroke: A meta-analysis" including 12 studies and 2269 stroke cases, analyzing the relationship between elevated baseline hs-CRP and stroke risk found that elevated CRP was an independent risk factor for stroke. The study proposes values <1.0 mg/L as low risk, 1.0 to 3.0 mg/L as intermediate risk, and >3.0 mg/L as high risk for cardiovascular disease and stroke in the Western society (12). In this thesis a cut-off value of >1.0 was selected for the chi-square tests, to exclusively investigate the intermediate and high-risk group for cerebral infarctions mentioned above. 21 participants were excluded due to levels >10 mg/L, and therefore possible acute or chronic inflammatory diseases (as done in 42% of other studies on low-grade elevated CRP-levels)(53). Despite excluding the low-risk group and analyzing only the intermediate and high-risk group we found no difference in presence of cerebral infarctions between participants with and without elevated baseline CRP.

The leading theory is that elevated CRP-levels are a marker for atherothrombotic disease and therefore can predict elevated risk of, among other conditions, cerebral infarctions(54). The HUNT3-MRI cohort has relatively good health, and possibly a better cerebrovascular risk profile than similar cohorts. This might make them less prone to atherothrombotic disease and possibly following cerebral infarctions. Modifications of cardiovascular risk, such as exercise, healthy diet, or statin treatment are described as effective CRP-lowering strategies(54). All are interventions that could be initiated following a clinical stroke. In that case, a baseline CRP-level that was elevated before a clinical stroke, might after the stroke be reduced back to normal due to treatment. This could have influenced our results, as clinical infarction patients could be registered without an elevated CRP-level.

For further investigation of the connection between CRP and increased risk of infarction, subclassification by level of low-inflammatory state (using hs-CRP) and analyses between different groups could be of great interest. One meta-analysis found that the risk of stroke was nearly 70% higher in healthy individuals with CRP in the highest quartile compared to

the lowest quartile(54). To be able to do this kind of analysis, several more participants might be needed to observe the trends at a population-level.

Further research and increased accessibility to hs-CRP are needed before low-grade elevated CRP-level can be of use clinically to calculate risk of cerebral infarction.

4.3 Strengths

The HUNT study is Norway's largest collection of health information about a general population(17). The broad specter of information collected in this study, makes it possible to investigate many different risk factors for cerebral infarctions found on MRI. Including clinical measures, blood samples and questionnaires from a general population over time it makes a good foundation for cross-sectional observational studies.

The HUNT study also separates from many previous studies of stroke in being performed on a general population determined by geographical area. In previous studies the populations investigated were selected due to type of insurance, workplace, the presence of a specific risk factor or the absence of, for example, stroke. This makes the HUNT MRI population a "true" Norwegian general population, less vulnerable to confounding. Furthermore, data collected from a Norwegian population are of great importance when planning the future Norwegian health care system as international data may not always be similar to the Norwegian situation(55).

Several different analyses were done in this thesis. Performing different analyses and having consistent findings across them strengthens the results. For example, hypertension was not a significant factor when comparing the group with and without hypertension or when investigating blood pressure as a continuous scale in the t-test or the binary linear logic regression model. In neither of the analyses, we found a significant link and the result will therefore be considered stronger.

This thesis is primarily an overall screening for associations between presence of cerebral infarction and a few selected, established modifiable and non-modifiable risk factors of stroke. The results in this thesis provide a status-quo and will hopefully be a valuable contribution to prospective follow-up studies of the HUNT3 MRI-cohort.

4.4 Limitations

This study has several limitations. It includes a few, selected variables that have been associated with increased risk of cerebral infarctions in other large studies. The HUNT3 MR-cohort was younger compared to the participants in these studies. In a younger cohort, other risk factors may be of more significance. Furthermore, only 40% of the cerebral infarctions reported in HUNT3 MR were clinical. Silent infarctions can possibly have a stronger association to different risk factors than clinical infarctions.

In the HUNT3 MRI-cohort there was a lower prevalence of both clinical and silent infarctions compared to previous clinical reports from the same geographical region and internationally(56,57). Only 2.8% of the HUNT MRI participants had silent infarctions, which is considerably lower than the ~4–28% reported in previous MRI studies(34,58). The HUNT3 MRI-cohort consists of volunteers and compared to both invited participants who choose not to be part of the MRI study and those not invited, they had a somewhat better cardiovascular risk profile, lower weight and higher education(26). One might speculate that this can explanation the lower number of infarctions. It can also be that the HUNT MRI cohort is not truly a “general” population (as planned for).

The low prevalence of strokes was also the source of another limitation. The low number of infarctions makes any kind of subclassification of the infarctions or participants difficult. Subclassification could perhaps give important or other new information about the risk factors associated with a specific patient group or infarction type or location (to a specific region of the brain).

The HUNT3 MRI-cohort had an age range from 50 to 66 years old. Out of all strokes in Norway only 8.1% occur in patients <55 years. This underlines the importance of follow-up studies of infarctions for example in the HUNT4 MRI data when it is completed. Our ultimate interest is in uncovering the possible life-time risk of cerebral infarction, rather than the cross-sectional incidence in participants who were relatively young and unlikely to have an infarction regardless of cerebrovascular risk profile.

Direct comparisons between cross-sectional observational studies of a general population and case-control studies are difficult. In cross-sectional designs in a general population the participants are not included prospectively, as in case-control studies. In case-control studies the participants can be included at the time of their first stroke incident. In HUNT3 MR both recent and previous cerebral infarction are analyzed as one group. This is challenging due to the medical preventive treatment and lifestyle intervention that should be initiated after a cerebrovascular event according to Norwegian guidelines (for example antihypertensive treatment or weight loss)(5). This can cause falsely low association between risk factors and cerebral infarctions, as the risk factors may be treated and not present at the time of the data collection in HUNT.

Another challenge with comparing our findings to results from large case-control studies, as the INTERSTROKE-study, is the recruitment of participants. In the INTERSTROKE-study and other case-control studies, recruited stroke patients from a hospital population(13). One significant difference between the general population in HUNT3 MRI and the hospitalized patients is the prevalence of silent and clinical infarctions. The hospitalized patients in the INTERSTROKE-study all had clinical strokes. In the HUNT3 MR-cohort approximately 60% of the infarctions were registered as silent infarctions. Silent infarctions may have a different risk profile than clinical infarctions, as mentioned above.

The HUNT3 MRI-cohort consisted of 1006 participants from a general population and out of these participants 40 persons were registered with a clinical or silent infarction. The effect of some risk factors tested might only be visible in large populations. Other large studies,

referred to in this thesis, have 10,000 or even 1 million participants and might therefore find statistically significant impact of risk factors with very small effects. Moreover, when analyzing some risk factors in this thesis, we did not have all information on all participants. It was approximately 5% missing cases across variables. When analyzing these together in the binary linear logic regression model, approximately 7.7% of the cases were missing. This reduces the statistical power.

The participants in the HUNT3 MRI-study have also participated in HUNT1, HUNT2 and HUNT3. Their physical and mental health has been measured in multiple rounds with clinical exams, physical tests, blood samples and questionnaires. Perhaps have this "routine" testing made some participants more aware of their own health status and inspired a healthier lifestyle. This could be some of the explanation as to why the HUNT3 MRI-cohort is quite healthy and perhaps have a better cerebrovascular risk profile and possibly reduced lifetime risk of cerebral infarction.

5. Conclusion

This medical student research thesis sought to contribute knowledge about different risk factors for cerebral infarctions in a general population (n=1006). In addition to risk factors identifiable with MRI (WMH and CM), several clinical and biological measurements were included. All selected variables had been found to be significant risk factors for cerebral infarctions in other large studies.

In this thesis the link between cerebral infarction and different possible risk factors were evaluated by implementing three different statistical analyzes. In the results, we found that age was significantly higher amongst the participants with cerebral infarction compared to infarction-free participants. An association between only excessive load of WMH and cerebral infarction were found in the binary logic regression model. Because both prevalence of cerebral infarction and load of WMH are known to be strongly related to

increasing age, it is possible that age was a confounder in the binary logic regression model. No other variables had a significant link to cerebral infarctions in our analyses.

In the fall of 2022, the MRI data from HUNT 4 will be ready and this paper can hopefully be a contribution to prospective follow-up studies of the HUNT3 MRI-cohort. Studies that possibly in time will benefit patients at an individual level, by identifying people at risk at an early stage and ultimately reduce the number of incidents and the morbidity associated with stroke.

6. Literature

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